See corresponding editorial on page 427.

# Dose response to vitamin D supplementation in African Americans: results of a 4-arm, randomized, placebo-controlled trial[1–4]

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## ABSTRACT

**Background:** Association studies have suggested that lower circulating 25-hydroxyvitamin D [25(OH)D] in African Americans may partially underlie higher rates of cardiovascular disease and cancer in this population. Nonetheless, the relation between vitamin D supplementation and 25(OH)D concentrations in African Americans remains undefined.

**Objective:** Our primary objective was to determine the dose-response relation between vitamin D and plasma 25(OH)D.

**Design:** A total of 328 African Americans in Boston, MA, were enrolled over 3 winters from 2007 to 2010 and randomly assigned to receive a placebo or 1000, 2000, or 4000 IU vitamin $D_3$/d for 3 mo. Subjects completed sociodemographic and dietary questionnaires, and plasma samples were drawn at baseline and 3 and 6 mo.

**Results:** Median plasma 25(OH)D concentrations at baseline were 15.1, 16.2, 13.9, and 15.7 ng/mL for subjects randomly assigned to receive the placebo or 1000, 2000, or 4000 IU/d, respectively ($P = 0.63$). The median plasma 25(OH)D concentration at 3 mo differed significantly between supplementation arms at 13.7, 29.7, 34.8, and 45.9 ng/mL, respectively ($P < 0.001$). An estimated 1640 IU vitamin $D_3$/d was needed to raise the plasma 25(OH)D concentration to ≥20 ng/mL in ≥97.5% of participants, whereas a dose of 4000 IU/d was needed to achieve concentrations ≥33 ng/mL in ≥80% of subjects. No significant hypercalcemia was seen in a subset of participants.

**Conclusions:** Within African Americans, an estimated 1640 IU vitamin $D_3$/d was required to achieve concentrations of plasma 25(OH)D recommended by the Institute of Medicine, whereas 4000 IU/d was needed to reach concentrations predicted to reduce cancer and cardiovascular disease risk in prospective observational studies. These results may be helpful for informing future trials of disease prevention. This trial was registered at clinicaltrials.gov as NCT00585637. *Am J Clin Nutr* 2014;99:587–98.

## INTRODUCTION

Beyond vitamin D's role in bone and calcium metabolism, prospective observational cohort studies have suggested inverse associations between circulating 25-hydroxyvitamin D [25(OH)D][5], which is the accepted measure of vitamin D status, and the incidence and mortality of cardiovascular disease (CVD) (1, 2), diabetes (3, 4), and several cancers (5–10). In 2011, the Institute of Medicine (IOM) updated Dietary Reference Intakes for vitamin D (11). A target 25(OH)D concentration of 20 ng/mL was recommended on the basis of studies of fracture risk in whites, which led to a Recommended Dietary Allowance (RDA) (defined as the daily amount needed to achieve 20 ng/mL in ≥97.5% of the population) of 600 IU/d for adults aged 19–70 y and 800 IU/d for adults aged >70 y.

A profound disparity in vitamin D status according to skin pigmentation has complicated the determination of an RDA. Compared with whites, African Americans have virtually one-half concentrations of 25(OH)D (12, 13), largely attributable to decreased vitamin D synthesis in skin with a greater melanin content (14). Consequently, the optimal dose of vitamin D to achieve adequate 25(OH)D concentrations in African Americans is unknown. Moreover, CVD and several cancers are more prevalent and have higher mortality in African Americans than whites (15, 16), and differences in plasma 25(OH)D could partly account for these disparities (17, 18).

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[2] Sponsors did not participate in the design or conduct of the study; collection, analysis, or interpretation of data; preparation, review, or approval of the manuscript; or decision to submit the article for publication. Contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute or NIH, Department of Defense, American Society of Clinical Oncology, or The Conquer Cancer Foundation.

[3] Supported by the National Cancer Institute at the NIH [P50CA127003; K07CA148894 (to KN); K22CA126992 (to GGB); 5K05CA124415 (to KME); and U01CA138962 (to PDC)], the Department of Defense Prostate Cancer Research Program [PC081669 (to BD)], an American Society of Clinical Oncology (ASCO) Career Development Award (to KN), and Pharmavite LLC.

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[5] Abbreviations used: CVD, cardiovascular disease; IOM, Institute of Medicine; PCP, primary care physician; RDA, Recommended Dietary Allowance; 25(OH)D, 25-hydroxyvitamin D.

Received August 5, 2013. Accepted for publication December 10, 2013.

First published online December 24, 2013; doi: 10.3945/ajcn.113.067777.

A critical need exists to quantify the vitamin D intake required by African Americans to achieve predefined targets of 25(OH)D. Therefore, we conducted a randomized clinical trial of 3 doses of vitamin $D_3$ and placebo in African Americans residing in public-housing communities to assess the dose-response relation in this population and identify the amount needed to raise 25(OH)D to specific predefined thresholds.

## SUBJECTS AND METHODS

### Study population and design

This study was a randomized, double-blind, placebo-controlled trial of vitamin $D_3$ supplementation in community-based African Americans (www.clinicaltrials.gov; NCT00585637). Participants were drawn from the Open Doors to Health, which is a colorectal cancer prevention study in 1554 subjects from 12 public-housing communities and community- and faith-based organizations in Boston (19). Subjects were 30–80 y old, understood written and spoken English, and self-identified as black or African American (20, 21). To minimize the contribution of UVB radiation to 25(OH)D concentrations (22), enrollment occurred from 31 December 2007 to 31 January 2008, 2 October 2008 to 31 March 2009, and 13 October 2009 to 31 March 2010. The derivation of the final cohort is shown in **Figure 1**. All subjects provided written consent, and the project was approved by institutional review boards of Harvard School of Public Health and Dana-Farber Cancer Institute.

Primary care physician (PCP) approval, which was sought after informed consent was obtained, was required to participate. Exclusion criteria included pregnancy, parathyroid, thyroid, or calcium disorders, sarcoidosis, a requirement for calcium channel blockers, type I diabetes, and concurrent active malignancies.

### Study treatment and assessments

Participants were assigned to 4 arms that consisted of a placebo or 1000, 2000, or 4000 IU vitamin $D_3$/d for 3 mo in a 1:1:1:1

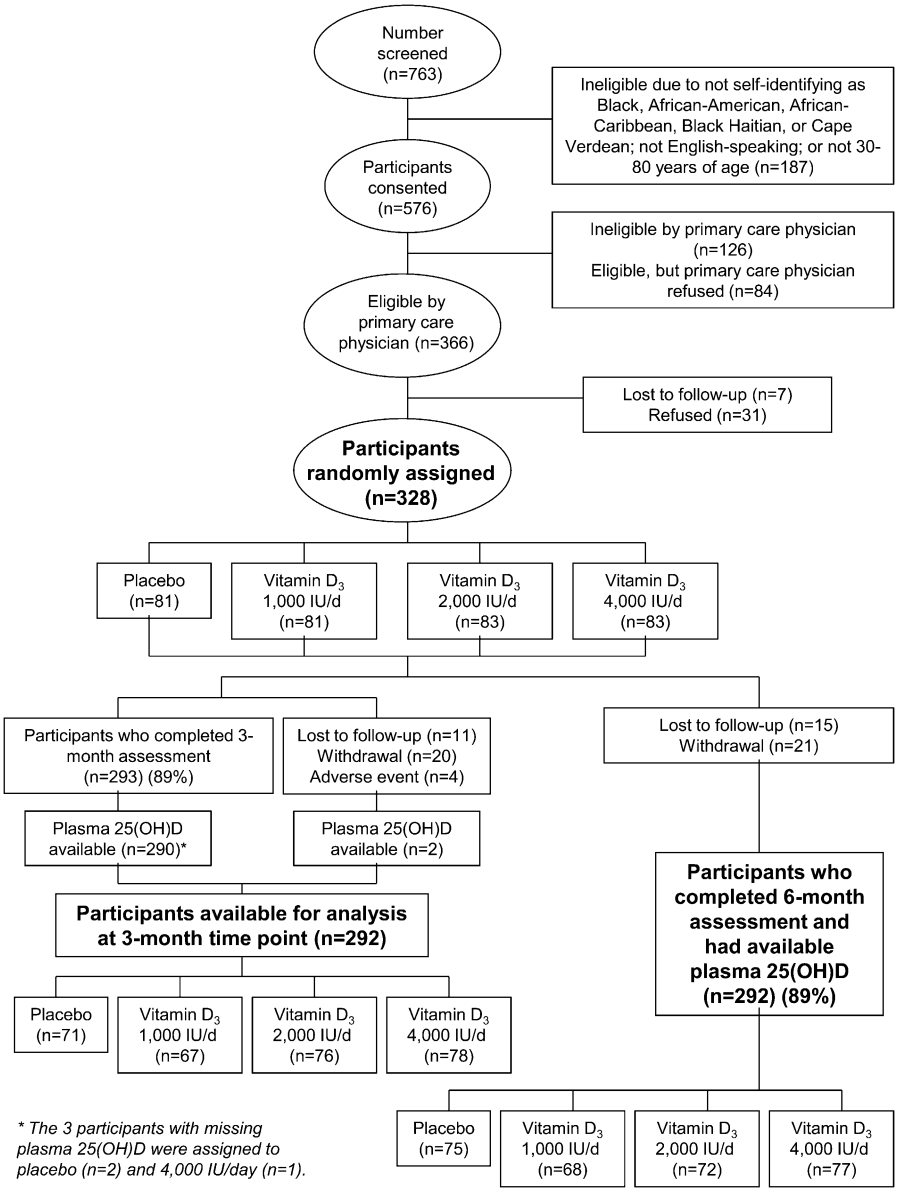


**FIGURE 1.** Consolidated Standards of Reporting Trials diagram. 25(OH)D, 25-hydroxyvitamin D.

ratio by using block random assignment stratified by age, sex, and enrollment month. Vitamin $D_3$ capsules were indistinguishable and also contained 100 mg Ca (Pharmavite LLC). Actual vitamin $D_3$ concentrations of capsules were 1291, 2557, and 5070 IU for 1000, 2000, and 4000 IU capsules, respectively, and the stability of capsules was confirmed at 3 y. Study statisticians generated the random allocation sequence, and subjects were enrolled by research assistants. All participants, providers, and study staff were blinded. Participants were followed for toxicity and compliance every 2 wk by phone and every 4 wk in person during supplementation. In addition, serum calcium was measured in subjects who were taking hydrochlorothiazide at 1 ($n$ = 79) and 3 ($n$ = 75) mo. Any subject shown to have a calcium concentration >10.5 mg/dL was immediately discontinued from the study, and the PCP notified. An additional subset of control participants, who did not take hydrochlorothiazide, also underwent calcium assays at 3 mo ($n$ = 44). Electronic pill-dispenser systems and pill counts were also used to track compliance with study supplementation. The study was monitored closely by a data and safety monitoring board composed of external advisors.

Plasma samples were collected in lavender-top evacuated tube containing liquid EDTA at baseline and 3 and 6 mo for 25(OH)D determination. Assays were performed in a single batch by using a radioimmunoassay (23) (DiaSorin Inc) in the laboratory of Bruce Hollis (Medical University of South Carolina, Charleston, SC). Masked quality-control samples were interspersed in cases and all laboratory personnel were blinded. The mean CV of the assay was 9%, and National Institute of Standards and Technology reference ranges (±SDs) were met as follows: concentration 1, 23.3 ± 1.8 ng/mL; concentration 2, 14.6 ± 1.3 ng/mL; concentration 3, 38.6 ± 2.4 ng/mL; and concentration 4, 33.1 ± 2.6 ng/mL. Participants were also asked to complete questionnaires at baseline and 3 and 6 mo that addressed socioeconomic and demographic factors, dietary and lifestyle behaviors, and medication use. Specifically, dietary vitamin D and calcium intakes were assessed by using questions modeled after the validated semifrequency food questionnaire (24).

Skin pigmentation was measured by using a tristimulus colorimeter device (Photovolt 577 Reflectometer; Photovolt Instruments Inc) (25–27). Measurements were done on the upper inner sides of both arms. Reflectance readings were converted to the Commission International d'Eclairage L*a*b* system, and the L* variable (range: 0–100 for white to black) was used to represent skin pigmentation (27). Twenty-five participants had outlier values for L* because of calibration errors that were imputed with the median in regression models.

### Study endpoints

The predefined primary endpoint was plasma 25(OH)D after 3 mo of supplementation, with the objective of identifying the dose of vitamin $D_3$ required to raise 25(OH)D concentrations to ≥33 ng/mL in ≥80% of participants in the intent-to-treat population, regardless of compliance. In a secondary analysis, the dose required to reach this threshold in compliant subjects (defined as subjects taking ≥75% of required pills) was determined. Although the protocol initially specified thresholds of 32 and 40 ng/mL for analysis, 33 ng/mL was ultimately chosen in consultation with the data and safety monitoring board on the basis of published observational studies that showed that individuals with 25(OH)D greater than this concentration had significantly lower risk of developing and dying from CVD and cancer (7–10, 28). Moreover, in light of the IOM report that recommended a target 25(OH)D concentration of 20 ng/mL in 2011 (11) and ongoing debate about the preferred 25(OH)D concentration, we sought to determine the daily intake of vitamin $D_3$ needed to achieve 20 ng/mL in 97.5% of the study cohort.

### Statistical analysis

Baseline characteristics of subjects were compared between supplementation arms by using Fisher's exact test (Monte Carlo method) for categorical variables and the Kruskal-Wallis test for continuous variables. We tested for a linear trend in median plasma 25(OH)D concentrations in each supplementation arm by performing a quantile regression at each time point. We calculated the percentage of participants with a plasma 25(OH)D concentration ≥33 ng/mL and identified the 25(OH)D concentration at the 20th percentile at 3 and 6 mo. To predict the dose needed to meet the IOM target of 20 ng/mL, a mixed model was used to estimate the best linear, unbiased predictor of within-subject mean plasma 25(OH)D concentrations (29). The mixed model used all available doses and time points and included a random patient effect to account for the within-subject correlation and estimate the variance of the mean within-subject concentration. For each time point, the model fit a quadratic effect of dose on the mean plasma 25(OH)D concentration greater than a dose of 1000 IU vitamin $D_3$/d and a single mean at dose 0 IU vitamin $D_3$/d. To calculate the dose required to achieve plasma 25(OH)D concentrations ≥20 ng/mL at 3 mo in ≥97.5% of the study cohort on the basis of this model, 1.96 times the SD of the mean within-subject concentration was subtracted from the estimated quadratic fit. This curve was used to interpolate to the dose expected to include 97.5% of future subjects' mean plasma 25(OH)D concentration >20 ng/mL. A 95% bootstrap percentile CI for the interpolated dose was calculated from 1000 bootstrap samples. The bootstrapping was stratified by dose, and the subject was the resampled unit.

In addition we explored predictors of plasma 25(OH)D by using linear regression. Variables evaluated in a stepwise selection included age, sex, year of study enrollment, skin pigmentation, BMI, exercise frequency, smoking status, regular multivitamin and vitamin D supplement use at baseline, dietary vitamin D intake, and baseline 25(OH)D. Individuals with missing data for any of these variables were excluded. We calculated the $P$-trend by using the vitamin $D_3$ dose as a continuous variable in the final multivariable model (8, 30). Statistical interactions between treatment arm and potentially modifying covariates were assessed by using Wald's test of cross-product terms.

The statistical power for this trial was based on the intent-to-treat population of 80 subjects/arm, regardless of compliance with the study treatment. During the study, the sample size was expanded to allow ≤100 participants/arm to account for *1*) the time gap between subject consent and PCP approval and *2*) a 10% withdrawal and lost-to-follow-up rate; however, this increase was ultimately not necessary. With the use of a 2-sided $t$ test at the 0.05 significance level, the minimum detectable difference in plasma 25(OH)D between treatment arms was 5.3 and 6.2 ng/mL with 80% and 90% power, respectively. For the secondary analysis in compliant participants, we had 80% power to detect a minimum

**TABLE 1**
Subject characteristics by supplementation arm[1]

| Characteristic | Vitamin $D_3$ dose assignment (for 3 mo) | | | | |
|---|---|---|---|---|---|
| | Placebo ($n$ = 81) | 1000 IU/d ($n$ = 81) | 2000 IU/d ($n$ = 83) | 4000 IU/d ($n$ = 83) | Total ($n$ = 328) |
| Age (y) | 50.7 (44.2, 58.0)[2] | 51.1 (43.4, 60.1) | 50.3 (43.4, 58.2) | 51.3 (44.1, 59.7) | 51.0 (43.6, 59.4) |
| Sex [$n$ (%)] | | | | | |
| M | 27 (33.3) | 22 (27.2) | 28 (33.7) | 29 (34.9) | 106 (32.3) |
| F | 54 (66.7) | 59 (72.8) | 55 (66.3) | 54 (65.1) | 222 (67.7) |
| Born in United States [$n$ (%)] | | | | | |
| Yes | 72 (88.9) | 69 (85.2) | 70 (84.3) | 67 (80.7) | 278 (84.8) |
| No | 9 (11.1) | 12 (14.8) | 12 (14.5) | 16 (19.3) | 49 (14.9) |
| Missing/unknown | 0 | 0 | 1 (1.2) | 0 | 1 (0.3) |
| Maximum education level [$n$ (%)] | | | | | |
| Less than high school | 16 (19.8) | 18 (22.2) | 23 (27.7) | 29 (34.9) | 86 (25.3) |
| High school degree | 32 (39.5) | 29 (35.8) | 23 (27.7) | 16 (19.3) | 100 (30.5) |
| Vocational/some college | 18 (22.2) | 19 (23.5) | 19 (22.9) | 25 (30.1) | 81 (24.7) |
| College degree | 12 (14.8) | 11 (13.6) | 14 (16.9) | 10 (12.1) | 47 (14.3) |
| Postgraduate degree | 3 (3.7) | 4 (4.9) | 3 (3.6) | 3 (3.6) | 13 (3.9) |
| Missing/unknown | 0 | 0 | 1 (1.2) | 0 | 1 (0.3) |
| Employment status [$n$ (%)] | | | | | |
| Working | 28 (34.6) | 31 (38.3) | 32 (38.6) | 31 (37.3) | 122 (37.2) |
| Not working | 53 (65.4) | 50 (61.7) | 51 (61.4) | 52 (62.7) | 206 (62.8) |
| Marital status [$n$ (%)] | | | | | |
| Married | 23 (28.4) | 30 (37.0) | 23 (27.7) | 24 (28.9) | 100 (30.5) |
| Not married | 58 (71.6) | 51 (63.0) | 59 (71.1) | 58 (69.9) | 226 (68.9) |
| Missing/unknown | 0 | 0 | 1 (1.2) | 1 (1.2) | 2 (0.6) |
| Median household income [$n$ (%)] | | | | | |
| <$10,000 | 33 (40.8) | 23 (28.4) | 27 (32.5) | 27 (32.5) | 110 (33.6) |
| $10,000–$19,999 | 15 (18.5) | 17 (21.0) | 17 (20.5) | 17 (20.5) | 66 (20.1) |
| $20,000–$29,999 | 11 (13.6) | 10 (12.3) | 16 (19.3) | 10 (12.0) | 47 (14.3) |
| $30,000–$39,999 | 4 (4.9) | 9 (11.1) | 4 (4.8) | 9 (10.8) | 26 (7.9) |
| $40,000–$49,999 | 4 (4.9) | 5 (6.2) | 4 (4.8) | 4 (4.8) | 17 (5.2) |
| ≥$50,000 | 9 (11.1) | 11 (13.6) | 11 (13.3) | 11 (13.3) | 42 (12.8) |
| Missing/unknown | 5 (6.2) | 6 (7.4) | 4 (4.8) | 5 (6.1) | 20 (6.1) |
| Skin tone ($n$ = 303) (L*)[3] | 45.1 (38.2, 50.4) | 44.9 (39.5, 50.2) | 44.4 (41.3, 50.7) | 44.6 (41.1, 48.4) | 44.7 (39.7, 50.1) |
| History of cancer [$n$ (%)][4] | | | | | |
| Yes[5] | 6 (7.4) | 6 (7.4) | 0 | 3 (3.6) | 15 (4.6) |
| No | 75 (92.6) | 74 (91.4) | 83 (100) | 79 (95.2) | 311 (94.8) |
| Missing/unknown | 0 | 1 (1.2) | 0 | 1 (1.2) | 2 (0.6) |
| History of hypertension [$n$ (%)] | | | | | |
| Yes | 35 (43.2) | 35 (43.2) | 36 (43.4) | 35 (42.2) | 141 (43.0) |
| No | 36 (44.4) | 33 (40.7) | 36 (43.4) | 34 (41.0) | 139 (42.4) |
| Missing/unknown | 10 (12.4) | 13 (16.1) | 11 (13.2) | 14 (16.8) | 48 (14.6) |
| No. of visits with doctor or nurse practitioner in past year | 3.0 (2.0, 6.0) | 4.0 (2.0, 5.0) | 3.0 (2.0, 5.0) | 3.0 (2.0, 5.0) | 3.0 (2.0, 5.0) |
| Smoking status [$n$ (%)] | | | | | |
| Never | 33 (40.7) | 36 (44.4) | 33 (39.8) | 44 (53.0) | 146 (44.5) |
| Past | 20 (24.7) | 16 (19.8) | 27 (32.5) | 20 (24.1) | 83 (25.3) |
| Current | 28 (34.6) | 29 (35.8) | 23 (27.7) | 19 (22.9) | 99 (30.2) |
| Postmenopausal hormone use [$n$ (%)][6] | | | | | |
| Yes | 1 (1.9) | 0 | 0 | 0 | 1 (0.5) |
| No | 37 (68.5) | 41 (69.5) | 30 (54.5) | 37 (68.5) | 145 (65.3) |
| Missing/unknown | 16 (29.6) | 18 (30.5) | 25 (45.5) | 17 (31.5) | 76 (34.2) |
| Travel to sunny region during supplementation period [$n$ (%)] | | | | | |
| Yes | 5 (6.2) | 4 (5.0) | 5 (6.0) | 7 (8.4) | 21 (6.4) |
| No | 68 (83.9) | 62 (76.5) | 70 (84.3) | 72 (86.8) | 272 (82.9) |
| Missing/unknown | 8 (9.9) | 15 (18.5) | 8 (9.7) | 4 (4.8) | 35 (10.7) |
| Frequency of exercise (d/wk)[7] ($n$ = 325) | 3.0 (0.5, 5.0) | 3.0 (1.0, 5.0) | 3.0 (0, 5.0) | 3.0 (0, 5.0) | 3.0 (0, 5.0) |
| BMI (kg/m$^2$) | | | | | |
| Baseline ($n$ = 325) | 31.2 (26.5, 35.9) | 30.5 (27.0, 37.5) | 31.9 (26.2, 36.9) | 31.4 (27.4, 35.7) | 31.2 (26.8, 36.3) |
| 3 mo ($n$ = 290) | 30.9 (26.3, 36.4) | 30.4 (26.6, 36.9) | 32.5 (27.2, 37.1) | 32.0 (27.1, 35.8) | 31.6 (26.5, 36.8) |
| 6 mo ($n$ = 291) | 31.8 (27.8, 37.0) | 29.9 (27.3, 37.3) | 32.5 (26.4, 37.1) | 30.9 (27.0, 35.1) | 31.0 (26.6, 36.9) |

*(Continued)*

**TABLE 1** (*Continued*)

| Characteristic | Vitamin $D_3$ dose assignment (for 3 mo) | | | | |
|---|---|---|---|---|---|
| | Placebo ($n$ = 81) | 1000 IU/d ($n$ = 81) | 2000 IU/d ($n$ = 83) | 4000 IU/d ($n$ = 83) | Total ($n$ = 328) |
| Dietary vitamin D intake (IU)[8] | | | | | |
| Baseline ($n$ = 328) | 147.3 (71.4, 262.8) | 162.5 (92.6, 295.5) | 144.0 (58.0, 265.1) | 198.1 (83.2, 306.4) | 167.5 (72.3, 291.8) |
| 3 mo ($n$ = 293) | 175.8 (93.7, 277.4) | 201.4 (81.0, 394.7) | 191.4 (93.3, 332.5) | 248.4 (134.5, 413.4) | 204.7 (93.7, 341.1) |
| 6 mo ($n$ = 292) | 181.5 (86.5, 307.9) | 209.3 (91.5, 308.2) | 251.8 (67.2, 405.8) | 245.3 (108.9, 398.1) | 227.1 (86.6, 368.6) |
| Dietary calcium intake (mg)[8] | | | | | |
| Baseline ($n$ = 328) | 277.0 (171.7, 632.3) | 422.9 (226.1, 795.9) | 318.8 (172.7, 637.4) | 445.9 (198.6, 780.4) | 356.6 (188.6, 693.8) |
| 3 mo ($n$ = 293) | 361.1 (198.6, 660.2) | 394.4 (169.8, 856.8) | 323.8 (197.8, 878.7) | 527.4 (256.9, 995.0) | 404.2 (197.8, 789.6) |
| 6 mo ($n$ = 292) | 342.7 (185.9, 769.5) | 430.2 (244.2, 886.6) | 420.3 (203.1, 836.4) | 453.3 (239.1, 825.9) | 424.6 (217.2, 799.9) |
| Regular multivitamin use [$n$ (%)][9] | | | | | |
| Yes | 10 (12.3) | 18 (22.2) | 15 (18.1) | 22 (26.5) | 65 (19.8) |
| No | 71 (87.7) | 63 (77.8) | 67 (80.7) | 61 (73.5) | 262 (79.9) |
| Missing/unknown | 0 | 0 | 1 (1.2) | 0 | 1 (0.3) |
| Regular vitamin D supplement use [$n$ (%)][9] | | | | | |
| Yes | 8 (9.9) | 6 (7.4) | 2 (2.4) | 8 (9.6) | 24 (7.3) |
| No | 72 (88.9) | 74 (91.4) | 81 (97.6) | 73 (88.0) | 300 (91.5) |
| Missing/unknown | 1 (1.2) | 1 (1.2) | 0 | 2 (2.4) | 4 (1.2) |
| Regular calcium supplement use [$n$ (%)][9] | | | | | |
| Yes | 7 (8.7) | 9 (11.1) | 7 (8.4) | 9 (10.8) | 32 (9.8) |
| No | 73 (90.1) | 71 (87.7) | 76 (91.6) | 74 (89.2) | 294 (89.6) |
| Missing/unknown | 1 (1.2) | 1 (1.2) | 0 | 0 | 2 (0.6) |
| Calendar month of enrollment [$n$ (%)] | | | | | |
| October | 14 (17.3) | 12 (14.8) | 14 (16.9) | 8 (9.7) | 48 (14.6) |
| November | 9 (11.1) | 7 (8.6) | 7 (8.4) | 11 (13.2) | 34 (10.4) |
| December | 15 (18.5) | 14 (17.3) | 14 (16.9) | 15 (18.1) | 58 (17.7) |
| January | 18 (22.2) | 24 (29.7) | 21 (25.3) | 20 (24.1) | 83 (25.3) |
| February | 11 (13.6) | 9 (11.1) | 11 (13.2) | 11 (13.2) | 42 (12.8) |
| March | 14 (17.3) | 15 (18.5) | 16 (19.3) | 18 (21.7) | 63 (19.2) |
| Year of study enrollment [$n$ (%)] | | | | | |
| 2007–2008 | 9 (11.1) | 13 (16.0) | 10 (12.0) | 13 (15.7) | 45 (13.7) |
| 2008–2009 | 45 (55.6) | 40 (49.4) | 42 (50.6) | 39 (47.0) | 166 (50.6) |
| 2009–2010 | 27 (33.3) | 28 (34.6) | 31 (37.4) | 31 (37.3) | 117 (35.7) |

[1] There were no significant differences in subject characteristics across supplementation arms except where indicated.
[2] Median; 25th, 75th percentiles in parentheses (all such values).
[3] L* is the lightness variable from the Commission International d'Eclairage (CIE) L*a*b* system, ranging from 0 to 100. Outlier values were imputed with the median value (see Subjects and Methods).
[4] $P$ = 0.03 (Fisher's exact test with the Monte Carlo method).
[5] Reported cancers include breast cancer, cervical cancer, uterine cancer, lung cancer, prostate cancer, and sarcoma.
[6] Percentages calculated from a total of 222 females.
[7] Exercise defined as moderate to vigorous physical activity for at least 30 min, resulting in a faster-than-normal heart rate, sweating, and deep breathing.
[8] Refers to the intake during the preceding month.
[9] Defined as supplement use for 7 d/wk during the preceding month.

between-arms rate difference of 0.26 [0.25 compared with 0.51 (ie, 25% of subjects who received 1000 IU vitamin $D_3$/d and attained plasma 25(OH)D concentrations ≥33 ng/mL compared with 51% of subjects who received 4000 IU/d vitamin $D_3$/d)] and >90% power to detect a rate difference of 0.30 (0.25 compared with 0.55) by using a 2-sided Fisher's exact test at the 0.05 significance level. All statistical analyses were performed with SAS 9.2 software (SAS Institute).

## RESULTS

Baseline characteristics for the 328 randomly assigned participants (222 women and 106 men) are presented in **Table 1**. More participants in the placebo and 1000-IU/d arms had a past history of cancer than did subjects who received 2000 or 4000 IU/d. Otherwise, there were no significant differences in any of the characteristics. In the 292 participants with available plasma 25(OH)D at 3 mo, relevant baseline characteristics were also similar between arms (data not shown). Compliance was high at 95.7%, 96.6%, 96.5%, and 97.6% for placebo and 1000-, 2000-, and 4000-IU/d arms, respectively, and did not differ significantly between arms ($P$ = 0.81).

### Impact of vitamin $D_3$ supplementation on plasma 25(OH)D

Plasma 25(OH)D concentrations at baseline and 3 and 6 mo are shown in **Table 2** and **Figure 2**. In 328 subjects, the median plasma 25(OH)D concentration at baseline was 15.3 ng/mL (25th,

**TABLE 2**
Plasma 25(OH)D concentrations by supplementation arm[1]

| Variable | Vitamin $D_3$ dose assignment (for 3 mo) | | | | Total | Effect estimate per 1000 IU vitamin $D_3$[2] | *P* |
|---|---|---|---|---|---|---|---|
| | Placebo | 1000 IU/d | 2000 IU/d | 4000 IU/d | | | |
| | | | | | | *ng/mL* | |
| Baseline plasma 25(OH)D (ng/mL) | 15.1 (10.4, 23.6)[3] | 16.2 (11.0, 22.7) | 13.9 (9.5, 22.3) | 15.7 (11.0, 23.3) | 15.3 (10.4, 22.8) | 0.12 ± 0.40 | 0.77[4] |
| Subjects (*n*) | 81 | 81 | 83 | 83 | 328 | — | — |
| Plasma 25(OH)D at 3 mo (ng/mL) | 13.7 (7.2, 18.6) | 29.7 (25.6, 32.9) | 34.8 (28.8, 41.0) | 45.9 (39.4, 55.2) | 31.7 (20.5, 41.8) | 8.00 ± 0.65 | <0.001[4] |
| Subjects (*n*) | 71 | 67 | 76 | 78 | 292 | — | — |
| Plasma 25(OH)D at 6 mo (ng/mL) | 18.1 (12.2, 23.3) | 21.2 (16.8, 27.8) | 27.0 (20.6, 31.1) | 31.2 (26.5, 35.9) | 24.6 (18.0, 31.2) | 3.28 ± 0.35 | <0.001[4] |
| Subjects (*n*) | 75 | 68 | 72 | 77 | 292 | — | — |
| Δ 3 mo to baseline plasma 25(OH)D (ng/mL) | −2.3 (−5.4, 1.7) | 10.8 (2.5, 18.9) | 19.3 (11.6, 26.2) | 30.3 (21.5, 37.6) | 15.0 (1.7, 25.1) | 8.60 ± 0.41 | <0.001[4] |
| Subjects (*n*) | 71 | 67 | 76 | 78 | 292 | — | — |
| Δ 6–3 mo plasma 25(OH)D (ng/mL) | 3.8 (0.9, 7.6) | −5.4 (−13.0, 0.3) | −9.4 (−14.4, −4.1) | −15.7 (−20.9, −9.8) | −7.2 (−14.5, 1.0) | −4.92 ± 0.35 | <0.001[4] |
| Subjects (*n*) | 69 | 67 | 71 | 76 | 283 | — | — |
| Plasma 25(OH)D ≥33 ng/mL at 3 mo [*n* (%)] | | | | | | — | <0.001[5] |
| Yes | 2 (2.5) | 16 (19.8) | 44 (53.0) | 73 (88.0) | 135 (41.1) | — | — |
| No | 69 (85.2) | 51 (63.0) | 32 (38.6) | 5 (6.0) | 157 (47.9) | — | — |
| Missing | 10 (12.3) | 14 (17.2) | 7 (8.4) | 5 (6.0) | 36 (11.0) | — | — |
| Plasma 25(OH)D ≥33 ng/mL at 6 mo [*n* (%)] | | | | | | — | <0.001[5] |
| Yes | 6 (7.4) | 6 (7.4) | 14 (16.8) | 29 (34.9) | 55 (16.8) | — | — |
| No | 69 (85.2) | 62 (76.5) | 58 (69.9) | 48 (57.8) | 237 (72.2) | — | — |
| Missing | 6 (7.4) | 13 (16.1) | 11 (13.3) | 6 (7.3) | 36 (11.0) | — | — |
| 20th percentile plasma 25(OH)D (ng/mL) | | | | | | | |
| 3 mo | 6.7 | 22.6 | 26.8 | 37.2 | 17.0 | — | <0.001[6] |
| 6 mo | 11.2 | 15.9 | 19.1 | 24.9 | 16.8 | — | <0.001[6] |

[1] 1 ng/mL = 2.496 nmol/L. 25(OH)D, 25-hydroxyvitamin D.
[2] All values are effect estimates ± SEs.
[3] Median; 25th, 75th percentiles in parentheses (all such values).
[4] *P*-linear trend in median plasma 25(OH)D concentration calculated by performing quantile regression.
[5] Calculated by using Fisher's exact test (Monte Carlo method).
[6] Calculated by using quantile regression.

75th percentiles: 10.4, 22.8) and did not differ significantly between arms ($P$-trend = 0.77). After 3 mo supplementation, 292 subjects (89.0%) provided plasma for follow-up 25(OH)D determination. Circulating plasma 25(OH)D concentrations at 3 mo differed significantly by supplementation arm, with medians of 13.7, 29.7, 34.8, and 45.9 ng/mL for placebo and 1000-, 2000-, and 4000-IU/d arms, respectively (effect estimate ± SE: 8.0 ± 0.65 ng/mL per 1000 IU vitamin $D_3$; $P$-trend $< 0.001$). Notably, plasma 25(OH)D decreased at 3 mo in subjects treated with the placebo. In the intent-to-treat population, the 4000-IU/d arm achieved plasma 25(OH)D concentrations ≥33 ng/mL in 88.0% of subjects compared with in 2.5%, 19.8%, and 53.0% of subjects for placebo and 1000- and 2000-IU/d arms, respectively ($P <$ 0.001). Correspondingly, the 20th percentile plasma 25(OH)D concentration in each of the supplementation arms was 6.7, 22.6, 26.8, and 37.2 ng/mL for placebo and 1000-, 2000-, and 4000-IU/d arms, respectively ($P < 0.001$). In comparison, the proportion of subjects in each arm who reached the IOM target of 20 ng/mL and The Endocrine Society target of 30 ng/mL (31) at 3 mo was 19.8%, 69.1%, 88.0%, and 92.8% and 3.7%, 37.0%, 63.8%, and 90.4%, respectively ($P < 0.001$ for both) (data not shown).

In 289 compliant participants, the 4000-IU/d dose remained the only arm that achieved the primary objective, with 93.4% of participants having a plasma 25(OH)D concentration ≥33 ng/mL. In contrast, only 2.8%, 23.9%, and 56.0% of compliant subjects who received the placebo or 1000 or 2000 IU/d, respectively, achieved 25(OH)D concentrations ≥33 ng/mL ($P < 0.001$) (data not shown).

At 6 mo, 292 subjects (89.0%) were available for plasma 25(OH)D determination. Plasma 25(OH)D differed significantly by supplementation arm, with medians of 18.1, 21.2, 27.0, and 31.2 ng/mL, respectively (effect estimate ± SE: 3.28 ± 0.35 ng/mL per 1000 IU vitamin $D_3$; $P$-trend $< 0.001$). Except for the placebo arm, median concentrations of 25(OH)D decreased compared with those at 3 mo, although not quite to baseline concentrations.

In light of the 2011 IOM report that established a 25(OH)D concentration of 20 ng/mL to be sufficient for bone health (11), we determined the dose of vitamin D required in our African American cohort to reach that threshold, similar to in previously published studies (32). The empirical Bayesian prediction interval to bound 97.5% of future subjects' mean plasma 25(OH)D concentrations intersected 20 ng/mL at 1640 IU/d (95% CI: 1490, 2020 IU/d) (**Figure 3**), which indicated that 97.5% of our population would maintain a mean plasma 25(OH)D concentration of 20 ng/mL at an estimated dosage of 1640 IU/d.

### Predictors of plasma 25(OH)D concentration and response to supplementation

We explored the impact of potential confounding variables on circulating 25(OH)D (**Table 3**). Age, regular multivitamin and vitamin D supplement use, smoking status, and year of study

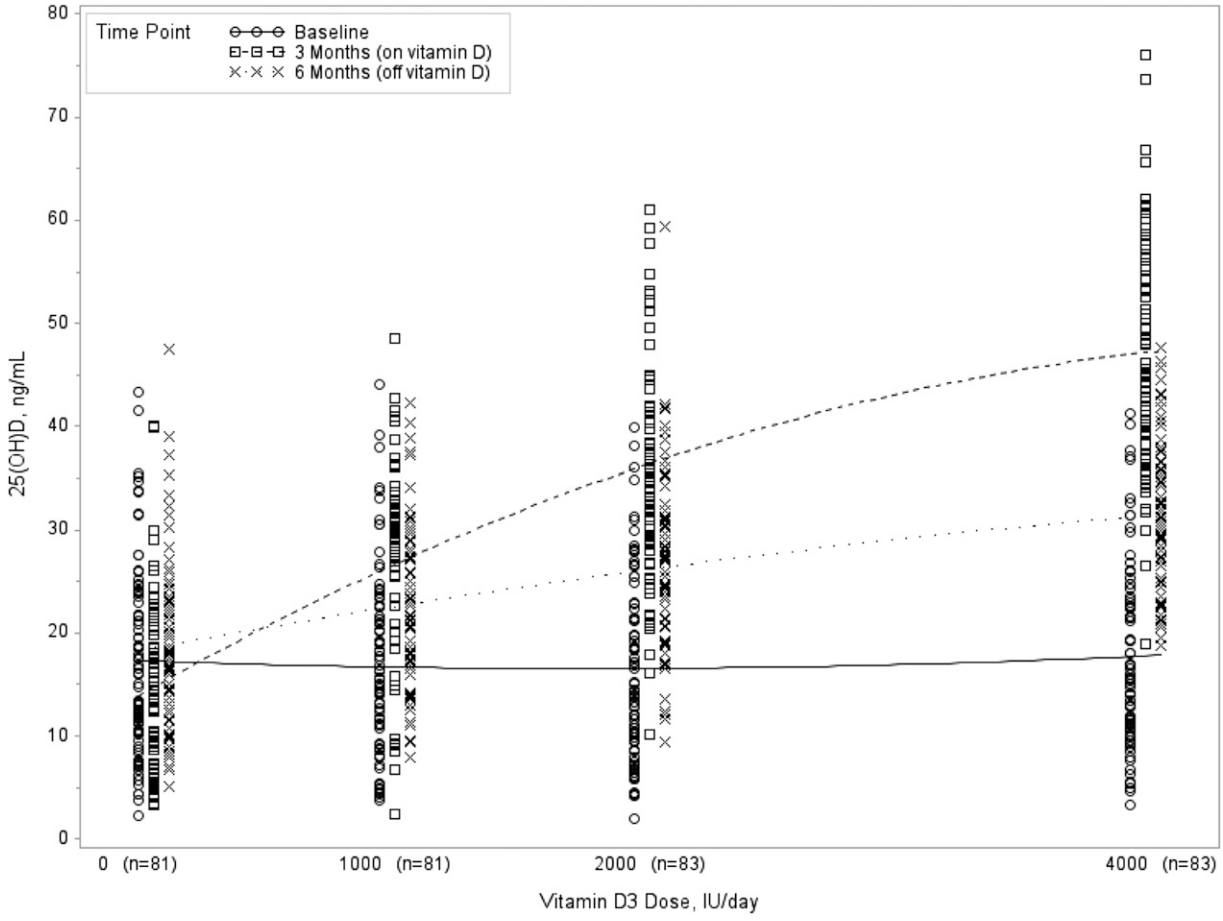


**FIGURE 2.** Plasma 25(OH)D concentrations (ng/mL) at baseline and 3 and 6 mo according to vitamin $D_3$ dose. 25(OH)D, 25-hydroxyvitamin D.

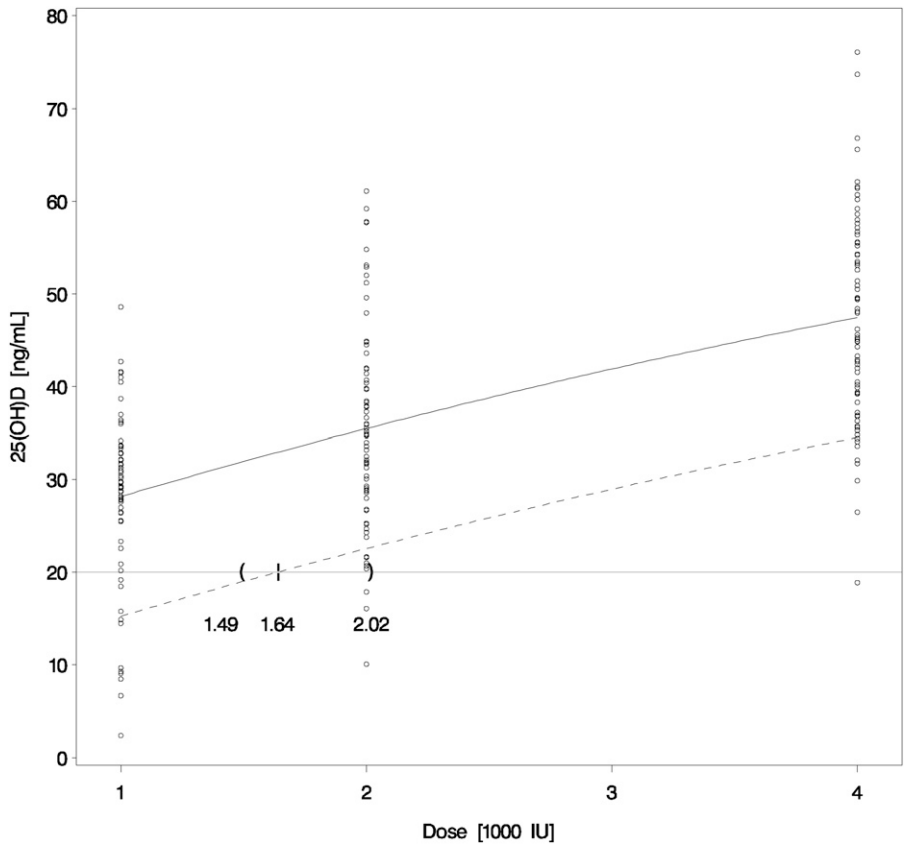


**FIGURE 3.** Graphical display of plasma 25(OH)D concentrations (ng/mL) at 3 mo and dose of vitamin $D_3$ supplementation ($n$ = 67 for 1000 IU/d; $n$ = 76 for 2000 IU/d; $n$ = 78 for 4000 IU/d). The solid line is a quadratic fit to the observed mean plasma 25(OH)D concentration. The dashed line falls below the mean line by 1.96 SDs of the distribution of the estimated within-subject mean concentration (obtained from the random patient effect in the mixed model) and represents the empirical Bayesian prediction interval to bound 97.5% of future subjects' mean plasma 25(OH)D concentrations. This prediction interval crosses the 20-ng/mL line at 1640 IU/d (95% CI: 1490, 2020 IU/d), indicating that an estimated dose of 1640 IU vitamin $D_3$/d is required to achieve an individual mean plasma 25(OH)D concentration at ≥20 ng/mL in ≥97.5% of the study population. 25(OH)D, 25-hydroxyvitamin D.

enrollment were significant independent predictors of baseline plasma 25(OH)D. Predictors of plasma 25(OH)D at 3 mo included the supplementation arm, baseline 25(OH)D, age, BMI, and year of enrollment, and predictors at 6 mo included the supplementation arm, baseline 25(OH)D, BMI, and year of enrollment. Of note, skin pigmentation was not an independent predictor of the 25(OH)D concentration at any time point.

We assessed whether any baseline characteristics modified the response to vitamin D supplementation. Current smokers, participants with lower BMI, and those who were not taking regular multivitamins or vitamin D supplements at baseline showed greater increases in plasma 25(OH)D per unit dose of vitamin $D_3$ (**Table 4**). Of note, baseline 25(OH)D was lower in many subgroups with a greater response, which was consistent with findings from other studies (33).

### Adverse events

Two subjects reported symptoms that were potentially attributable to hypercalcemia (pruritis and polydipsia with polyuria), but subsequent calcium assays were normal. At 1 mo, 79 participants who were taking hydrochlorothiazide were required to have calcium concentrations checked. At 3 mo, 119 participants had serum calcium assayed, 75 (63.0%) subjects of whom were taking hydrochlorothiazide. There were no significant differences in calcium concentrations between arms at 1 mo ($P$ = 0.14) and 3 mo ($P$ = 0.52) (*see* Supplemental Table 1 under "Supplemental data" in the online issue). In 128 participants with available calcium at either time point, 5 subjects (3.9%) were shown to have concentrations >10.5 mg/dL (range: 10.7–11.2 mg/dL), and all of them were asymptomatic and taking hydrochlorothiazide. Four subjects had elevated calcium at 1 mo and were discontinued from the study per protocol (3 subjects were receiving 1000 IU/d, and one subject was receiving 2000 IU/d). The fifth subject was assigned to receive 4000 IU/d and had elevated calcium at 3 mo at the conclusion of supplementation and, therefore, was kept in the final analysis.

## DISCUSSION

In community-based African Americans in Boston, supplementation with 4000 IU vitamin $D_3$/d for 3 mo resulted in 88.0% of subjects achieving plasma 25(OH)D concentrations ≥33 ng/mL, whereas an estimated 1640 IU/d was required for ≥97.5% of subjects to reach 20 ng/mL. Hypercalcemia was not seen at these doses in a subset of participants with available data, which was consistent with the 2011 IOM report (11). To our knowledge, this is the largest randomized, placebo-controlled trial to evaluate vitamin D dosing in African Americans.

Our study filled an important knowledge gap because previous randomized trials of vitamin D have been largely confined to

**TABLE 3**
Predictors of plasma 25(OH)D concentrations at various time points from a multiple linear regression model by using stepwise selection[1]

| Covariate | Effect estimate[2] | *P* |
|---|---|---|
| | *ng/mL* | |
| Baseline ($n$ = 323) | | |
| Age (y) | 0.17 ± 0.04 | <0.0001 |
| Regular vitamin D supplement use at baseline[3] | | |
| No | Referent | — |
| Yes | 8.34 ± 1.72 | <0.0001 |
| Regular multivitamin use at baseline[3] | | |
| No | Referent | — |
| Yes | 5.57 ± 1.17 | <0.0001 |
| Smoking status | | |
| Current | Referent | — |
| Past | 1.75 ± 1.15 | 0.13 |
| Never | 2.28 ± 1.01 | 0.02 |
| Year of study enrollment | | |
| 2007–2008 | Referent | — |
| 2008–2009 | 3.38 ± 1.29 | 0.009 |
| 2009–2010 | 4.43 ± 1.34 | 0.001 |
| 3 mo ($n$ = 290) | | |
| Supplementation arm[4] | | |
| Placebo | Referent | — |
| 1000 IU vitamin $D_3$/d | 13.93 ± 1.43 | <0.0001 |
| 2000 IU vitamin $D_3$/d | 21.39 ± 1.39 | <0.0001 |
| 4000 IU vitamin $D_3$/d | 32.46 ± 1.38 | <0.0001 |
| Baseline plasma 25(OH)D (ng/mL) | 0.44 ± 0.06 | <0.0001 |
| Age (y) | 0.08 ± 0.04 | <0.001 |
| BMI (kg/m$^2$) | −0.14 ± 0.06 | 0.04 |
| Year of study enrollment | | |
| 2007–2008 | Referent | — |
| 2008–2009 | 0.95 ± 1.49 | 0.52 |
| 2009–2010 | 3.62 ± 1.57 | 0.02 |
| 6 mo ($n$ = 290) | | |
| Supplementation arm[5] | | |
| Placebo | Referent | — |
| 1000 IU vitamin $D_3$/d | 3.33 ± 1.06 | 0.002 |
| 2000 IU vitamin $D_3$/d | 8.01 ± 1.04 | <0.0001 |
| 4000 IU vitamin $D_3$/d | 11.98 ± 1.02 | <0.0001 |
| Baseline plasma 25(OH)D (ng/mL) | 0.52 ± 0.04 | <0.0001 |
| BMI (kg/m$^2$) | −0.18 ± 0.05 | 0.0003 |
| Year of study enrollment | | |
| 2007–2008 | Referent | — |
| 2008–2009 | −2.44 ± 1.14 | 0.03 |
| 2009–2010 | −0.84 ± 1.18 | 0.48 |

[1] All values are effect estimates ± SEs. 1 ng/mL = 2.496 nmol/L. Variables evaluated by using stepwise selection included age, sex, year of study enrollment, skin pigmentation, BMI at baseline, exercise frequency at baseline, smoking status, regular multivitamin use at baseline, regular vitamin D supplement use at baseline, dietary vitamin D intake at the relevant time point, travel to a sunny region during the preceding 3 mo (3- and 6-mo analyses only), and baseline plasma 25(OH)D concentration (3- and 6-mo analyses only). Variables were selected for inclusion in the model if $P \leq 0.10$. The treatment arm was forced into the model in the 3- and 6-mo analyses. 25(OH)D, 25-hydroxyvitamin D.

[2] All values are effect estimates ± SEs.

[3] Defined as supplement use 7 d/wk during the preceding month.

[4,5] Calculated by using the vitamin $D_3$ dose as a continuous variable in the multiple linear regression model: [4] $P$-trend < 0.001, [5] $P$-trend = 0.10.

whites and have included few, if any, African Americans. A recent trial randomly assigned 163 postmenopausal white women with 25(OH)D concentrations ≤20 ng/mL to 7 doses of vitamin $D_3$ compared with a placebo for 12 mo and determined the RDA to be 800 IU/d for a target of 20 ng/mL and 1600 IU/d for a target of 30 ng/mL (32). The authors subsequently published results of 79 postmenopausal African American women within their study and showed that the RDA was similar to that for whites at 800 IU/d for the IOM target of 20 ng/mL and 1600 IU/d for 30 ng/mL (34). In contrast, in a separate trial of 79 younger African American women conducted by the same group, an estimated RDA of 1200 IU/d was reported (35), which was more consistent with our findings. Potential reasons for the disparate results, despite similar statistical methods, included a much smaller sample size, lower baseline 25(OH)D concentrations, different age groups, and a longer period of supplementation in the Gallagher et al (32, 34) populations compared with in the current study.

Our findings are relevant in light of the 2011 IOM report that recommended an RDA of 600 IU/d for adults ≤70 y old to achieve a target 25(OH)D concentration of 20 ng/mL on the basis of studies of hip fractures in whites (11). The IOM acknowledged that additional research was needed to clarify the vitamin D dose-response relation and impact on skeletal health in African Americans. High rates of vitamin D deficiency have long been well documented in African Americans (36). Beyond differences in the melanin content, disparities in BMI and lifestyle behaviors also contribute with higher rates of obesity (37), lower intake of vitamin D-rich foods (38), and less sun exposure (39) in African Americans. An underlying germline variation in genes associated with vitamin D metabolism may also play a role (EM Awumey, BW Hollis, NH Bell, AW Norman, R Bouillon, and M Thomasset, unpublished observations, 1997) (40). Indeed, data have suggested that serum concentrations of vitamin D–binding protein are significantly lower in African Americans than whites (41, 42), which lead to lower total 25(OH)D concentrations.

However, the clinical significance of low 25(OH)D in African Americans is unknown because the frequency of fractures is lower in this population (43, 45). Possible explanations for this relation include anatomical differences in hip geometry, with increased femoral cortical thickness and a shorter hip-axis length compared with in whites (44) and a blunted skeletal response to parathyroid hormone that leads to lower rates of bone resorption (45). Other potential factors area higher bone mineral density (46) and prevalence of obesity (43). Indeed, a randomized, placebo-controlled trial of vitamin D in 208 African American women reported no beneficial effect on bone mineral density after 3 y of treatment (47).

Independent of bone health, observational studies have implicated vitamin D as a mechanism that potentially underlies racial disparities in CVD and cancer (17, 18), although this hypothesis is still controversial. In large, prospective cohort studies of predominantly white populations, a 25(OH)D concentration ~33 ng/mL has been associated with decreased CVD and cancer risk and improved survival (7–10, 28). In the NHANES III cohort, participants with 25(OH)D concentrations ≥37 ng/mL had a lower prevalence of several cardiovascular risk factors (28). In contrast, a randomized, placebo-controlled, clinical trial of elderly women reported higher rates of falls and fractures with massive yearly doses of vitamin $D_3$ (500,000 IU) compared with a placebo, and an observational study reported increased risk of pancreatic cancer with 25(OH)D concentrations ≥40 ng/mL. Therefore, the IOM concluded that the effect of vitamin D on

**TABLE 4**
Response in plasma 25(OH)D concentrations to vitamin $D_3$ supplementation across strata of selected variables[1]

| Subgroup | Subjects | Median plasma 25(OH)D at baseline | Median plasma 25(OH)D at 3 mo | Increase (±SE) in Δ plasma 25(OH)D per 1000 IU vitamin $D_3$/d[2] | *P*-trend[3] | *P*-interaction[4] |
|---|---|---|---|---|---|---|
| | *n* | *ng/mL* | *ng/mL* | *ng/mL* | | |
| Age[5] | | | | | — | 0.42 |
| <51.0 y | 142 | 12.8 | 31.3 | 7.45 ± 0.50 | <0.0001 | — |
| ≥51.0 y | 150 | 18.5 | 32.2 | 8.01 ± 0.49 | <0.0001 | — |
| Sex | | | | | — | 0.97 |
| M | 92 | 13.3 | 32.0 | 7.76 ± 0.62 | <0.0001 | — |
| F | 200 | 16.0 | 31.7 | 7.73 ± 0.42 | <0.0001 | — |
| Skin tone[5] | | | | | — | 0.82 |
| <44.7 L* | 134 | 15.1 | 32.2 | 7.73 ± 0.51 | <0.0001 | — |
| ≥44.7 L* | 137 | 14.2 | 31.7 | 7.56 ± 0.50 | <0.0001 | — |
| Smoking status | | | | | — | 0.006 |
| Current | 82 | 12.8 | 29.0 | 9.37 ± 0.67 | <0.0001 | — |
| Never or past | 210 | 16.7 | 32.2 | 7.20 ± 0.40 | <0.0001 | — |
| Travel to sunny region during preceding 3 mo | | | | | — | 0.56 |
| Yes | 21 | 20.3 | 33.6 | 8.45 ± 1.22 | <0.0001 | — |
| No or unknown | 269 | 14.4 | 31.7 | 7.70 ± 0.36 | <0.0001 | — |
| Frequency of exercise at baseline[5] | | | | | — | 0.22 |
| <3.0 d/wk | 119 | 14.0 | 30.4 | 7.18 ± 0.54 | <0.0001 | — |
| ≥3.0 d/wk | 170 | 16.5 | 32.0 | 8.07 ± 0.46 | <0.0001 | — |
| BMI at baseline | | | | | — | 0.03 |
| <30 kg/m$^2$ (nonobese) | 130 | 15.5 | 32.6 | 8.62 ± 0.52 | <0.0001 | — |
| ≥30 kg/m$^2$ (obese) | 160 | 14.5 | 31.6 | 7.08 ± 0.45 | <0.0001 | — |
| Dietary vitamin D intake reported at 3 mo[5] | | | | | — | 0.56 |
| <204.7 IU | 145 | 13.0 | 30.4 | 7.99 ± 0.50 | <0.0001 | — |
| ≥204.7 IU | 145 | 17.0 | 32.9 | 7.59 ± 0.49 | <0.0001 | — |
| Regular multivitamin use at baseline[6] | | | | | — | 0.02 |
| Yes | 58 | 23.4 | 34.3 | 6.20 ± 0.77 | <0.0001 | — |
| No | 233 | 13.3 | 31.3 | 8.15 ± 0.39 | <0.0001 | — |
| Regular vitamin D supplement use at baseline[6] | | | | | — | 0.02 |
| Yes | 21 | 26.8 | 29.7 | 5.20 ± 1.13 | <0.0001 | — |
| No | 267 | 14.0 | 31.7 | 8.06 ± 0.36 | <0.0001 | — |
| Year of study enrollment | | | | | — | 0.26 |
| 2007–2008 | 45 | 14.0 | 31.4 | 8.44 ± 0.91 | <0.0001 | — |
| 2008–2009 | 166 | 15.1 | 30.3 | 7.11 ± 0.49 | <0.0001 | — |
| 2009–2010 | 117 | 17.1 | 34.3 | 8.32 ± 0.57 | <0.0001 | — |

[1] 1 ng/mL = 2.496 nmol/L. L*, lightness variable from the Commission International d'Eclairage (CIE) L*a*b* system, ranging from 0 to 100; 25(OH)D, 25-hydroxyvitamin D.
[2] Adjusted for age, year of study enrollment, BMI at baseline, baseline 25(OH)D concentration, and the covariate for which subgroups were being explored.
[3] Calculated by using vitamin $D_3$ dose as a continuous variable in the multiple linear regression model.
[4] Calculated by using Wald's test of cross-product terms.
[5] Cutoff defined by the median value.
[6] Defined as supplement use for 7 d/wk during the preceding month.

cancer, immune disorders, and CVD has not been sufficiently established. An ongoing study, the Vitamin D and Omega-3 Trial (VITAL), is comparing 2000 IU vitamin $D_3$/d to a placebo for disease prevention with a planned oversampling of African American participants.

Our study had several strengths. The randomized, placebo-controlled design allowed for an objective assessment of effects of the vitamin $D_3$ dose on plasma 25(OH)D while controlling for confounding factors. Serum calcium concentrations were monitored, and no adverse effects were seen. Pill compliance and follow-up rates for blood draws and questionnaires were also high. There was minimal confounding of the effect of vitamin D supplementation by UVB exposure because the study was conducted in the Northeastern United States during winter, travel to sunnier regions was infrequent, and regular supplement use at baseline was low. The limited use of vitamin D supplements after the treatment period also allowed us to examine the natural trend in plasma 25(OH)D once supplementation ended. Finally, our study was able to quantify skin pigmentation in subjects and showed that it was not a significant predictor of plasma 25(OH)D.

Several limitations also deserve comment. Our cohort was supplemented for only 3 mo, which could have affected the estimation of

the dose needed to reach certain thresholds of plasma 25(OH)D, and the endpoint of the study was not the long-term benefit of supplementation, which is currently being addressed by the Vitamin D and Omega-3 Trial (VITAL). However, data have suggested that a steady state of 25(OH)D is reached at 3 mo (48). Indeed, in a study of 50 colorectal cancer patients treated with 2000 IU vitamin D/d for 6 mo, the mean 25(OH)D concentration was 31.6 ng/mL at 3 mo and did not increase substantially at 6 mo (mean: 33.8 ng/mL) (49). Although we selected a target plasma 25(OH)D concentration ≥33 ng/mL on the basis of prospective observational studies, clinical trials that have assessed the effect of achieving this concentration are not available to our knowledge. In addition, we studied only 3 doses of vitamin $D_3$, with the highest being 4000 IU/d; therefore, we were not able to evaluate the influence of more-intermediate or higher doses on plasma 25(OH)D concentrations.

In conclusion, in African Americans residing in a public-housing community, 1640 IU vitamin $D_3$/d was necessary to achieve a target plasma concentration 25(OH)D of 20 ng/mL, whereas 4000 IU/d was needed to raise plasma 25(OH)D to a concentration potentially associated with reduced cancer and CVD risk in selected prospective observational studies. These findings may be helpful when designing future studies of disease prevention in African Americans.

We thank the following members of the data and safety monitoring board for their contributions to the project and manuscript: Debra Prothrow-Stith, John A Baron, and Caren G Solomon. We also thank Walter C Willett for his input on the design of the study, data interpretation, and manuscript. We gratefully acknowledge the efforts of the Vitamin D Research Team (Jennifer Bido, Christian Brown, Tamara Buchanan, Lindsay Cloutier, Molly Coeling, Ruth Lederman, Kamala Loscocco, Yudy Muneton, Bianka Recinos, Sanghamitra Savadatti, and Qi Wang) and Dana-Farber Cancer Institute phlebotomists (Jean Epps and Merline McKenzie). Finally, we thank the Resident Service Coordinators at collaborating housing sites, Maxi Hudson from Jubilee Christian Church, and all participants in the study.

The authors' responsibilities were as follows—KN, BFD, ATC, PDC, GGB, ELG, JAM, KME, and CSF: designed the research; KN, JBS, BFD, ATC, BWH, PDC, EG-S, KME, and CSF: conducted the research; JBS, EG-S, KME, and CSF: provided essential materials and subjects; KN, JBS, ELG, KME, and CSF: wrote the manuscript; KN: had primary responsibility for the final content of the manuscript; and all authors: analyzed data and read and approved the final manuscript. BWS has received support from DiaSorin SpA for serving as an academic consultant. KN, JBS, BFD, ATC, PDC, GGB, ELG, EG-S, JAM, KME, and CSF reported no conflicts of interest.

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